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Adding gentamicin to fluoroquinolone-based antimicrobial prophylaxis reduces transrectal ultrasound-guided prostate biopsy-related infection rate

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ABSTRACT

Objective: Transrectal ultrasound-guided prostate (TRUS) biopsy is the standard method for the diagnosis of prostate cancer. Quinolone-based prophylaxis before a TRUS biopsy of the prostate is the most common regimen worldwide. In this retrospective study, we evaluated the efficacy and cost effectiveness of adding gentamicin to a fluoroquinolone-based prophylaxis regimen.

Materials and methods: In total, our study included 263 patients classified into two groups. Group 1 consisted of 129 patients who received one oral dose of levofloxacin (500 mg) daily 2 days before the biopsy, on the day of the biopsy, and for 2 days after the biopsy. Group 2 consisted of 134 patients who received a single intramuscular (IM) gentamicin injection (80 mg) 30 minutes before the biopsy in addition to the same oral levofloxacin protocol as Group 1. We recorded and analyzed data including age, indication for a TRUS biopsy of the prostate, prostate volume, comorbidity, infectious complications, and blood and urine culture results.

Results: The mean prostate-specific antigen level was 38.6 ng/mL ± 312.9 ng/mL (range, 4.4–2626 ng/mL) in Group 1, and 34.8 ng/mL ± 127.1 ng/mL (range, 2.11–1423 ng/mL) in Group 2. The groups were similar in terms of mean age, indication for a biopsy, prostate volume, number of biopsy cores taken, and comorbidities. Infection-related complications occurred in eight of 129 (6.2%) and in one of 134 (0.74%) patients in Groups 1 and 2, respectively ($p = 0.02$).

Conclusion: The addition of IM gentamicin (80 mg) was beneficial in improving the efficacy of fluoroquinolone and reducing the post-TRUS biopsy infection rate. Gentamicin is relatively inexpensive and readily available in daily practice and has good compliance for patient use.

1. Introduction

Transrectal ultrasound-guided prostate (TRUS) biopsy is the standard method for the diagnosis of prostate cancer.[1] It is generally a safe procedure with acceptable complication rates. Infectious complications after a prostate biopsy include fever, urinary tract infections, acute bacterial prostatitis, epididymo-orchitis, and sepsis.[2] The reported incidence of urinary tract infections after a TRUS biopsy typically ranges between 2% and 6%, with approximately 30–50% of these patients exhibiting accompanying bacteremia.[3,4] Bacteremia is frequently accompanied by severe sepsis, which has a reported overall incidence of 0.1–2.2% following a TRUS biopsy.[3] A Canadian study reported increasing rates of hospitalization within a 30-day period following a TRUS biopsy, from 1.0% in 1996 to 4.1% in 2005 ($p < 0.0001$).[5] Similarly, using data derived from Medicare records, researchers from the United States also reported an increasing frequency of infectious complications following a TRUS biopsy, increasing from 0.4% in 1991 to 1.1% in 2007 ($p < 0.0001$).[6] Therefore, reducing the postbiopsy infection rate is a challenge in the TRUS biopsy era.

Fluoroquinolone is one of the most commonly used prophylactic antibiotics for TRUS biopsies and has been used in our hospital for the past years. The American Urological Association guidelines for

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the use of prophylactic antibiotics for a TRUS biopsy of the prostate state that all recommended antibiotics are acceptable in the outpatient setting.[7] Furthermore, Western countries have reported and recommend aminoglycosides in combination with metronidazole, or fluoroquinolones and cephalosporins for TRUS biopsies. The incidence of prostate cancer varies from one country to another, with the highest incidence being found in the Western world and the lowest in Asian countries.[8] Therefore, owing to the relatively low incidence of prostate cancer, there could be different views regarding the feasibility and cost effectiveness of such formula used in Asian countries.

In this study, we compared infectious complication rates in patients undergoing a TRUS biopsy of the prostate who were given prophylactic levofloxacin only with those given levofloxacin combined with a single dose of intramuscular (IM) gentamicin (80 mg) to evaluate the efficiency of adding IM gentamicin to standard prophylaxis in reducing infection-related complications after a TRUS biopsy.

2. Materials and methods

We conducted this retrospective study from January 2008 to August 2011. The charts of patients who received a TRUS biopsy in this period were reviewed. The patients who did not receive levofloxacin as a prophylactic antibiotic were excluded. Patient's history was reviewed, including age, diabetes mellitus (fasting plasma glucose level ≧ 130 mg/dL), hypertension (blood pressure ≧ 140/90 mmHg), and other comorbidities. In total, the study included 263 patients. Group 1 consisted of 129 patients who received one oral dose of levofloxacin (500 mg) daily 2 days before the biopsy, on the day of the biopsy, and for 2 days after the biopsy. Group 2 consisted of 134 patients who received a single IM gentamicin injection (80 mg) 30 minutes before the biopsy in addition to the same oral levofloxacin protocol as Group 1. Whether or not to add gentamicin as an adjunctive is decided by the attending doctor.

The indications for a TRUS biopsy included elevated prostate-specific antigen (PSA) level (>4 ng/mL), abnormal digital rectal examination, findings in a first prostate biopsy that necessitated a repeat biopsy such as the presence of an atypical gland or persistent elevation of PSA.

Almost all of the patients received the TRUS biopsy as an outpatient procedure except those who came for consultation for prostate biopsy during admission. Urine analysis, coagulation profile, and serum creatinine were all examined before the TRUS biopsy. Bowel movements were ensured with Bisacodyl (Dulcolax) suppositories given the previous night, and all patients had a cleansing enema before the procedure. With the patient in the left decubitus position, the TRUS biopsy was performed by an urologist with a multiplanar, multifrequency probe (75 MHz) attached to an ultrasound scanner. The prostate volume was calculated using the prostate ellipsoid formula: volume (V) = 0.52 ($L \times W \times H$), where L is the cephalocaudal diameter, W is the width, and H is the anteroposterior diameter. The patients with superhigh PSA levels demonstrating osteoblast bone metastasis received 10 cores prostate biopsy; all other patients received 12–16 cores biopsy. The prostate biopsies were taken with an 18-gauge × 20-cm needle with an automated spring loaded gun mechanism (Bard Biopsy Gun). The biopsies were obtained at the apex, middle, and base of the bilateral prostate lobes in the parasagittal plane.

The patients were informed to return to the hospital if they developed a fever (>38.5°C), chills, or newly developed severe lower urinary tract symptoms and macroscopic hematuria with blood clots. The patients who experienced the aforementioned symptoms within 14 days of the procedure in the absence of other clinically apparent sources of infection were defined as having "post-TRUS biopsy infection-related complications."

Mean and standard deviations were determined. These two groups were compared with respect to descriptive characteristics and factors before and after biopsy using the Chi-square, Fisher exact test, and the student t test. A p value ≦0.05 was considered statistically significant.

3. Results

The characteristics of patients in the two groups are listed in Table 1. They were similar in terms of mean age (68.4 years ± 8.747 years in Group 1 and 69.20 years ± 10.394 years in Group 2), indication for biopsy, prostate volume (32.65 mL ± 10.82 mL in Group 1 and 35.46 mL ± 12.35 mL in Group 2), and the number of biopsy cores taken. The mean PSA level was 38.653 ng/mL ± 312.9249 ng/mL (range, 4.4–2626 ng/mL) in Group 1, and 34.843 ng/mL ± 127.1309 ng/mL (range, 2.11–1423 ng/mL) in Group 2. The percentage of patients with hypertension and diabetes was 31% (40/129) and 17% (22/129) in Group 1, 34.3% (46/134) and 14.9% (20/134) in Group 2, respectively. The comorbidities are comparable in both groups.

As shown in Figure 1 and Table 1, infection-related complications occurred in eight of 129 (6.2%) and one of 134 (0.74%) patients in Groups 1 and 2, respectively (p = 0.02). Table 2 shows the possible etiological risk factors (including antibiotic prophylaxis, diabetes mellitus, hypertension, age, prostate cancer, and biopsy core number) and predisposing infection-related complications after a prostate biopsy. There was no statistically significant association between comorbidities including diabetes, hypertension, age, biopsy core number, and the pathology with postbiopsy infection-related complications, except antibiotics prophylaxis.

The patients with infection-related complications were hospitalized for intravenous antibiotics treatment. All organisms isolated were tested for antibiotic susceptibility to second- and third-generation cephalosporins as shown in Table 3. Over our study period, there were four blood cultures and one urine culture that were positive for *Escherichia coli* in nine cases of post-TRUS biopsy-related sepsis. Three of the four positive blood cultures were resistant to levofloxacin with only one exhibiting sensitivity. Of the four positive blood cultures, three were sensitive to gentamicin.

4. Discussion

Currently, TRUS biopsy of the prostate remains the most common procedure for the detection of prostate cancer. Although the procedure is generally considered to be safe and well-tolerated, postbiopsy complications are reported in up to 50% of cases, including pain, hematuria, hematospermia, urinary retention, and infection.[9] Septicemia is the most dangerous complication following the procedure and requires emergency admission and administration of intravenous antibiotics. The most common pathogen implicated in post-TRUS biopsy sepsis is *E. coli*, accounting for approximately 75–90% of infectious complications in published series.[10] In our fluoroquinolones-only prophylactic group, infection-related complications occurred in eight of 129 (6.2%) patients, which was comparable with previous reports.[3,4] Our results indicated that fluoroquinolones were effective as prophylaxis for TRUS prostate biopsies in 86.6% of patients. *E. coli* was the only causative organism identified in our positive cultures. Over our study period, there were four positive blood cultures and one positive urine culture in nine cases of post-TRUS biopsy-related sepsis. This finding is consistent with other reports, and thus, we directed our antibiotic prophylactic treatment at *E. coli*. Tal et al[2] also identified *E. coli* as the most common pathogen in their series.

Table 1
Patient characteristics from both groups.

	Levo-only group	Levo + GM group	*p*
No. of patients	129	134	N/S
Age (y)	68.4 ± 8.747	69.20 ± 10.394	N/S
PSA (ng/mL)	38.653 ± 112.9249 (4.4–2626)	34.843 ± 127.1309 (2.11–1423)	N/S
Total prostate volume (mL)	32.65 ± 10.82	35.46 ± 12.35	N/S
No. of biopsy core	12.4 ± 1.4	12.7 ± 1.6	N/S
DM	22	20	N/S
Hypertension	40	46	N/S
Infection-related complications	8/129 (3.0%)	1/134 (0.4%)	0.02
prostate cancer	29	36	N/S

Levo = levofloxacin; DM = diabetes mellitus; GM = gentamicin; N/S = not significant; PSA = prostate-specific antigen.

A recent systematic review of relevant studies concluded that antimicrobial prophylaxis was effective in preventing infectious complications following a prostate biopsy. Fluoroquinolones, sulfonamides, and other classes of antibiotics have been reported to be effective compared with a placebo; however, most reports favor the use of fluoroquinolones.[11] Nevertheless, fluoroquinolone-resistant *E. coli* isolates were found to have increased in the past decades. Our results also showed the high incidence (three fourth) of fluoroquinolone-resistant *E. coli* isolated from post-TRUS biopsy infection cases, which is consistent with the report by Feliciano et al.[12] The rates of resistant *E. coli* isolates in the United States were reported to be 0% in 1998 and 12% in 2007, whereas in the United Kingdom, the reported rates were 1% in 1994 and 23% in 2006.[13] In pursuit of ideal antibiotic prophylactic treatment, various regimens have been used with no clear consensus among urologists. Rodriguez and Terris[14] used IM gentamicin if the patient had valvular heart disease.[14] Ho et al[15] also reported that the addition of IM gentamicin was effective in improving the efficacy of levofloxacin in reducing the incidence of sepsis. Our results also support the fact that the addition of gentamicin is beneficial in reducing the post-TRUS biopsy infection-related complication rate. Targeted therapy of prophylaxis as opposed to empirical prophylaxis had been reported in recent years. The targeted prophylactic antibiotics used before prostate biopsy were based on the sensitivity of bacteria isolated from rectal swabs of each patient. Such regimens were demonstrated to be highly efficacious in reducing infection complication after prostate biopsy.[16] A disadvantage of targeted therapy is that it is expensive and time consuming compared with our regimen.

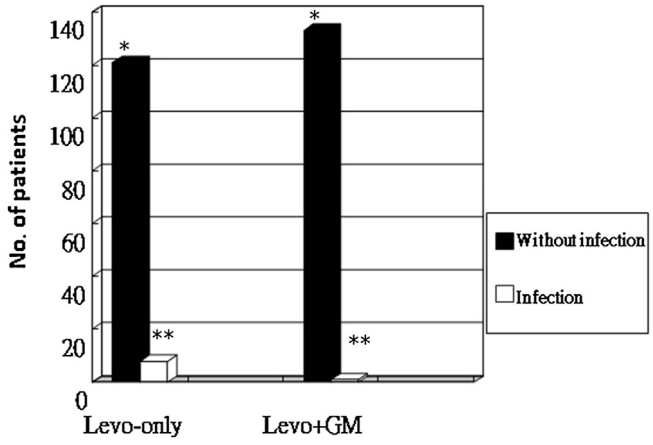

Figure 1. Bar graph demonstrates the infection related to TRUS prostate biopsy in the levofloxacin-only and levofloxacin combined with gentamicin groups. GM = gentamicin; Levo = levofloxacin; TRUS = transrectal ultrasound. $^{*}p > 0.05$, $^{**}p = 0.02$.

Table 2
Prophylaxis and potential risk factors predisposing infectious complications after prostate biopsy.

Risk factor	Total	Infection		*p*
		No	Yes	
Prophylaxis				0.02
Levo only	129 (49.0)	121 (46.0)	8 (3.0)	
Levo + GM	134 (51.0)	133 (50.6)	1 (0.4)	
Hypertension				0.610
No	177 (67.3)	171 (65.0)	6 (2.3)	
Yes	86 (32.7)	83 (31.6)	3 (1.1)	
DM				0.538
No	219 (83.3)	211 (80.2)	8 (3.0)	
Yes	44 (16.7)	43 (16.3)	1 (0.4)	
Pathology				0.074
BPH	198 (75.3)	189 (71.9)	9 (3.4)	
CaP	65 (24.7)	65 (24.7)	0 (0)	
Age (y)				0.168
<60	43 (16.3)	40 (15.2)	3 (1.1)	
≧60	220 (83.7)	214 (81.4)	6 (2.3)	
No. of biopsy core				0.176
10–12	233 (88.6)	224 (85.2)	9 (3.4)	
>12	30 (11.4)	30 (11.4)	0 (0)	

Data presented as numbers, with percentages in parentheses.
BPH = benign prostatic hyperplasia; CaP = prostate carcinoma; DM = diabetes mellitus; GM = gentamicin; Levo = levofloxacin.

Table 3
Microbiologic characteristics of the isolates and susceptibility of antibiotics.

Patient	1	2	3	4	5	6	7	8	9
Urine culture	N	N	N	N	N	N	N	N	P
Urine microorganism									*E. coli*
Blood culture	N	N	N	N	P	N	P	P	P
Blood microorganism					*E. coli*		*E. coli*	*E. coli*	*E. coli*
Antibiotic sensitivity									
Ampicillin					R		R	S	I
Amoxicillin/clavulanic					R		R	S	S
Piperacillin					S		S	S	S
Cefazolin					R		S	S	S
Ceftazidime					S		S	S	S
Ceftriaxone					S		S	S	S
Cefepime					S		S	S	S
Ciprofloxacin					R		R	S	R
Levofloxacin					R		R	S	R
Imipenem					S		S	S	S
Ertapenem					S		S	S	S
Meropenem					S		S	S	S
Amikacin					S		S	S	S
Gentamicin					R		S	S	S
Trimethoprim/sulfamethoxazole					R		R	R	R
Piperacillin/tazobactam					S		S	S	S

E. coli = *Escherichia coli*; I = intermediate; N = negative; P = positive; R = resistant; S = susceptible.

Several recent studies have attempted to identify both patient and procedural factors that may predict which men are at greatest risk of infectious complications.[6,12,14] The risk factors identified are underlying medical comorbidities, particularly diabetes mellitus, hypertension, recent hospitalization, and number of biopsy cores. Our study does not confirm the association between comorbidities and biopsy infection-related complication. Although one study found that an increased number of cores taken during the biopsy procedure was associated with postbiopsy infection,[17] other studies have not confirmed this association.[10,18,19] Our data also demonstrates that those with increased biopsy cores have no statistically significant higher postbiopsy infection-related complication rates.

In addition to efficacy in preventing infections, the cost effectiveness and clinical applicabilities of a regimen should be considered. In a survey of 900 practicing American urologists, only 3.3% used a combination of oral and IM prophylactic antibiotics.[20] Shigemura et al[21] reported that isepamicin plus fluoroquinolone can be considered a valuable regimen for antibiotic prophylaxis in TRUS biopsies. Batura et al[22] reported that adding amikacin to fluoroquinolone-based antimicrobial prophylaxis in areas with high fluoroquinolone resistance confers significant benefits in preventing infections after a TRUS biopsy.[22] A single dose of gentamicin (80 mg) is relatively cheap (each vial costs US$ 0.15), readily available, and appropriate for outpatient clinical application. Gentamicin's pharmacokinetics suggests that the drug plays a prophylactic role as well. The 30-minute lag time between IM injection and TRUS biopsy allows for maximal serum bioavailability at the time of the procedure, which agrees with the principle of surgical antibiotic prophylaxis. A recent randomized trial demonstrated that a piperacillin/tazobactam (2.25 g) prophylactic regimen for 2 days for TRUS biopsies of the prostate resulted in a lower incidence of bacteriuria and febrile urinary tract infections compared with oral ciprofloxacin.[23] Because of the high cost and patient compliance with piperacillin/tazobactam, prophylaxis with quinolones plus IM gentamicin in patients undergoing a TRUS biopsy of the prostate seems to be a better choice and has cost benefits.

However, the increasing rate of aminoglycoside resistance is another issue in the prevention of post-TRUS biopsy infectious complications, and aminoglycoside resistance is commonly encountered alongside fluoroquinolone resistance and extended spectrum beta-lactamase production.[24] Awareness of aminoglycoside resistance is another issue when considering the appropriate choice of empiric treatment for patients presenting to hospital with post-TRUS biopsy infections, particularly given that some recent guidelines advocate aminoglycosides for the empiric treatment of urosepsis.[25] In addition, due to the renal toxic effects of gentamicin, it is not recommended in patients with marked renal function impairment.

Our study has several limitations. First, there is uncertainty regarding patient compliance with the oral intake of prophylactic antibiotics as prescribed. Second, some of the infectious complications may not have been related to the prostate biopsy. In addition, the retrospective nature of the study design and nonrandomization of the study groups are also limitations.

The European Association of Urology guideline recommended a single-dose prophylaxis for low-risk patients and a prolonged course for high-risk patients.[25] Despite the relatively high comorbidities, including diabetes mellitus and hypertension, in our study groups, our protocol, levofloxacin daily 2 days before the biopsy, on the day of the biopsy, and for 2 days after the biopsy, still had room to be adjusted. Further research is warranted to establish the utility and cost effectiveness of adding gentamicin or other combinations of antibiotics in prophylaxis for TRUS biopsies.

In conclusion, our preliminary results demonstrate that the addition of IM gentamicin (80 mg) is beneficial in improving the efficacy of fluoroquinolones and reducing the post-TRUS biopsy infection rate. Gentamicin is relatively inexpensive and readily available in daily practice with good compliance for patient use, except in patients with marked renal function impairment. Once a post-TRUS biopsy-related infection is noted, third- or fourth-generation cephalosporins, carbapenem, or piperacillin/tazobactam are the recommended empirical treatments.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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